REMARKS

The Applicants thank the Examiner for the courtesy of an interview, conducted on December 14, 2004. At the close of the interview, the Examiner prepared an Interview Summary Form which was signed by Applicant's representative and which indicates that Applicant need not provide a summary.

Applicants petition for a three-month extension of time. A separate petition accompanies this document.

I. Amendments

Claims 60-70 are cancelled without prejudice of Applicants' right to pursue the claims in a continuing application.

II. Rejection Under 35 U.S.C. 112, First Paragraph

Claims 21-22, 25-32, and 57-59 were rejected under 35 U.S.C. 112, first paragraph as allegedly failing to comply with the written description requirement. Specifically, the Examiner asserts the words "micellar suspension" in claim 21 lacks support in the specification as originally filed. The Examiner was unable to find the expression 'micellar suspension' at the locations Applicants noted (page 29, lines 16-19 and page 9, lines 25-29).

The Examiner is directed to page 29, lines 16-19 which reads:

> "....of the invention includes a plurality of targeting conjugates in the form of pre-filled vials containing the conjugate as a purified, sterile **micellar suspension** in an appropriate buffer."

On page 9, lines 25-29 the application states:

> "....The targeting conjugates and pre-formed liposome pluralities are shown in **suspension** form in vial ready for use..."

While the citation on page 9, lines 25-29 does not use the word "micellar", the targeting conjugates when in "suspension form" are inherently in micellar form.

The Examiner is also directed to the following locations in the specification that describe a micellar solution or micellar suspension of the targeting conjugates:

Page 36, line 30 ("At various time points, targeting conjugates (micelles) were separated from inserted targeting conjugates (liposomes) by....")

Page 37. line 7 ("where the peak centered around fraction 10 corresponds to the liposomes and the peak centered around fraction 30 corresponds to the **micellular**, targeting conjugates.")

Page 38, line 13 ("the concentration of the Fab-PEG-DSPE **micellular solution**...")

Page 39, line 26 ("The pre-formed liposomes were incubated with the **micellular solution of the targeting conjugate**....")

Thus, the words "micellar suspension" are based in the application as originally filed. Withdrawal of the rejection under 35 U.S.C. 112, first paragraph is respectfully requested.

III. Double Patenting Rejections

Claims 21-22, 25-32, 57-70 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of Patent No. 6,120,798 (hereinafter 'the 798 patent').

Claims 21-22, 25-32, 57-70 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of Patent No. 5,891,468 (hereinafter 'the '468 patent).

Claims 21-22, 25-32, 57-70 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 66-69 of Application serial no. 10/115,566.

Applicants respectfully traverse these rejections for the following reasons.

A. Analysis of the Rejection Based on the '798 Patent

The issue of double patenting was addressed in *In re Vogel* (422 F2d 438, 164 USPQ 614 (Fed. Cir. 1970)), where, for obviousness-type double patenting, *Vogel* asks: "Does any claim in the application define merely an obvious variation of an invention disclosed and claimed in the patent?". The question seeks to determine if the invention of

the pending application is a mere variation (which would have been obvious to those of ordinary skill in the art) of an already claimed invention.

The claims of the '798 patent relate to a liposome composition comprised of a suspension of liposomes having an inner coating of a cationic lipid and an outer coating of neutral lipids, the liposomes prepared according to a recited process. Claim 6 specifies that the liposomes can include a neutral lipid derivatized with a hydrophilic polymer; claim 9 specifies that the hydrophilic polymer is PEG. Claim 8 recites that the liposomes can also include a ligand for targeting.

The claims of the '798 patent are directed to a liposome composition and nowhere describe or suggest a micellar suspension of a lipid-polymer-ligand conjugate. Such a suspension would not be used to make the targeted liposomes per claim 8 of the '798 patent, so it cannot be seen how the Applicants claims to a micellar suspension of a lipid-polymer-ligand conjugate would be an obvious variation of the claims of the '798 patent.

Thus, withdrawal of the rejection is respectfully requested.

B. Analysis of the Rejection Based on the '468 Patent

The claims of the '468 patent relate to a liposome composition comprised of a suspension of liposomes having an entrapped therapeutic agent, the liposomes containing a lipid derivatized with a copolymer (hydrophobic block/hydrophilic block). Claim 8 includes all of these features, plus the limitation of a ligand attached to the hydrophilic block of the copolymer.

The claims of the '468 patent are directed to a liposome composition and do not show or suggest a micellar suspension of a lipid-polymer-ligand conjugate.

Thus, withdrawal of the rejection is respectfully requested.

C. Analysis of the Rejection Based on Pending 10/115,566

The claims of the 10/115,566 application are directed to a method of preparing of liposome composition. The claims are not related to a micellar suspension of a targeting conjugate. Thus, withdrawal of the rejection is respectfully requested.

IV. Rejection under 35 U.S.C. § 102

Claims 21-22, 25-26, 57, and 60-61 were rejected under 35 U.S.C. §102(b) as being anticipated by Zalipsky *et al.*, WO 94/21281. This rejection is respectfully traversed for the following reasons.

A. The Present Invention

The present invention relates to a micellar suspension comprising a plurality of targeting conjugates for use in preparing a targeted, therapeutic liposome composition, each conjugate consisting essentially of (i) a lipid having a polar head group and a hydrophobic tail, (ii) a polyethylene glycol polymer having a proximal end and a distal end, said polymer attached at its proximal end to the head group of the lipid, and (iii) a targeting ligand having binding affinity for a receptor expressed on a cell attached to the distal end of the polymer.

B. The Applied Art

Zalipsky *et al.* disclose a polypeptide attached to a particle support (such as a liposome). In one embodiment, the polypeptide is attached with a PEG chain to a liposomal lipid (Fig. 1B; page 8, lines 15-25). The polypeptide is attached to the liposome support by reacting the polypeptide with a liposome-bound lipid, the lipid having a polar head group (which can be a hydrophilic polymer) activated for attachment with the polypeptide.

Thus, formation of the liposome-bound polypeptide does not involve formation of a micellar suspension of a lipid-polymer-ligand conjugate. The liposome-bound lipid-polymer is activated for reaction with the polypeptide after liposome formation (page 16, lines 5-14). Page 18, lines 21-26 summarize that the polypeptide is coupled to the free ends of PEG spacer arms carried on the liposome surface.

C. Analysis

The standard for lack of novelty, that is, for anticipation, is one of strict identity. To anticipate a claim for a patent, a single prior source must contain all its essential elements. M.P.E.P. § 2131.

Instant claims require a micellar suspension of a lipid-polymer-ligand conjugate. As noted above, Zalipsky *et al.* do not teach such a suspension. Nor are the liposome-bound polypeptides described in Zalipsky *et al.* formed from a micellar suspension of a lipid-polymer-ligand conjugate. As described on page 16, lines 5-14 and on page 18, lines 21-16 the polypeptide is coupled to the free ends of PEG chains already bound to the liposome surface.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102.

V. Rejections under 35 U.S.C. § 103

Claims 21-22, 25-32, and 57-70 were rejected under 35 U.S.C. §103 as being obvious over Zalipsky *et al.* (WO 94/21281).

Claims 30-32, 57-59, 65, and 67-70 were rejected under 35 U.S.C. §103 as being obvious over Zalipsky *et al.* (WO 94/21281) in view of Kilpatrick *et al.* (U.S. Patent No. 4,913,902).

Claims 28-29, 32, 63-64, and 67 were rejected under 35 U.S.C. §103 as being obvious over Zalipsky *et al.* (WO 94/21281) in view of Margalit (U.S. Patent No. 5,603,872).

These rejections are respectfully traversed for the following reasons.

A. The Cited Art

Zalipsky *et al.* are described above.

Kilpatrick *et al.* describe a method for extracting a desired compound from a solution using liposomes bearing a ligand that binds with the compound. The ligand is covalently coupled to the phospholipid (Col. 3, line 66 to Col. 4, line 6).

Margalit describes liposomes having various adhesive substances, such as epidermal growth factor, gelatin, collagen, and hyaluronic acid, bound to the liposome surface, to render the liposomes "sticky" for targeting to a designated site.

B. Analysis: Rejection over Zalipsky *et al.* alone and in combination with Kilpatrick *et al.* or Margalit

According to M.P.E.P. § 2143, "to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations."

Zalipsky *et al.* nowhere show or suggest a micellar suspension of a lipid-polymer-ligand conjugate. The liposome-bound polypeptides described in Zalipsky *et al.* are formed by attaching the polypeptide to the reactive end of a liposome-bound polymer chain (page 16, lines 5-14 and on page 18, lines 21-16). Thus, Zalipsky *et al.* does not contemplate formation of a lipid-polymer-conjugate as a separate species, let alone as a micellar suspension.

Kilpatrick describes liposomes having a ligand attached directly to the lipid head group. The reference nowhere shows or suggests a micellar suspension of a lipid-polymer-ligand conjugate.

Margalit describes liposomes having a 'recognizing substance' attached directly to the lipid head group. The reference nowhere shows or suggests a micellar suspension of a lipid-polymer-ligand conjugate.

Because the cited documents, alone or in combination, do not show all of the claim limitations, as required by M.P.E.P. § 2143, the claims are not obvious in view of the cited documents. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103.

VI. Conclusion

In view of the foregoing, the claims pending in the application comply with the requirements of 35 U.S.C. § 112 and patentably define over the applied art. A Notice of Allowance is, therefore, respectfully requested.

If the Examiner has any questions or believes a telephone conference would expedite prosecution of this application, the Examiner is encouraged to call the undersigned at (650) 838-4402.

Respectfully submitted,

Date: December 17, 2004

Judy M. Mohr
Registration No. 38,563

Correspondence Address:
Customer No. 22918
Phone: (650) 838-4300